SMMGP CLINICAL UPDATE

February 2011

Decreased bone density in men on methadone maintenance therapy. *Grey A, Rix-Trott K, Horne A, Gamble G, Bolland M, Reid IR. Addiction 2011;106:349-354*

Commentary on Grey et al. (2011): Does methadone maintenance therapy adversely effect bone mass. *Nakchbandi IA. Addiction 2011;106:355-56*

This study in New Zealand took 83 people who had taken methadone maintenance therapy for periods ranging from 6-16 years (median 11 years). They had a relevant history taken – including such factors as history of fractures, smoking history, menstrual history in women, current medication especially past use of glucocorticoids or osteoporotic medications, and dietary calcium intake.

They then measured bone mineral density (BMD) at lumbar spine, total hip and total body. These data were compared to age and gender matched data from an Australian osteoporosis study. They also compared the data with baseline measurements in 40 healthy men who had been recruited for another study looking at bone disease in HIV infection.

The results showed that in men BMD was lower than normal at each skeletal site (mean Z-score -1.1 with 95% CI -1.6 to -0.7). This was significant (P<0.001) at each site. In women there was no significant difference. It was also noted that serum testosterone was lower in men taking methadone than in the controls.

SMMGP comment: Osteoporosis is a disease that we need to consider increasingly in opioid-dependent populations, as the drug using population ages. We need to turn our gaze to a wider range of issues and, like any medication, methadone has the potential for long-term side effects. What now seems to be obvious is that we need to add skeletal health to the list of medical problems to consider in men. The reduction in bone density in men (but not in women) translates into a risk of fractures that is doubled.

It is easy to think of a considerable number of additional factors in an opioid dependent population that could be significant contributors to decreased bone density – poor nutrition, lack of exercise, and higher alcohol and tobacco use. What would the BMD be like in those not in treatment but with opioid dependence? We simply don't know. This is a cross-sectional study and limited as a snapshot in time. There is even the possibility that these results represent an improvement compared with men not in treatment. The authors acknowledge this and highlight the need for a longitudinal study to tease out the issues. In the meantime, whatever the cause assessing and addressing osteoporosis in the group should be considered.

Changes in blood-borne infection risk among injection drug users. Mehta SH, *Astemborski J, Kirk GD, et al. J Inf Diseases 2011;203:587-594*

Prevention of hepatitis C virus in injecting drug users: a narrow window of opportunity. *Grebely J, Dore GJ. J Inf Diseases 2011;203:571-574*

This month the Journal of Infectious Diseases carried an article and commentary on hepatitis C and injecting drug users (IDUs) with the article reporting on one aspect of the AIDS Linked to the Intravenous Experience (ALIVE) study that follows a community-based cohort of IDUs in Baltimore in the USA. Nearly 3000 IDUs were enrolled in 1988-89 and were followed up at 6-month intervals. The cohort was 'replenished' with further periods of recruitment in 1994-5, 1998 and 2005-2008.

This aspect of the study took those participants who had given a serum sample for HCV antibodies at baseline. They then took 250 random people from this sub-cohort and each participant had blood taken and completed

questionnaires exploring injecting behaviours, treatment episodes and other factors associated with their substance use.

The results showed a dramatic decline in HIV infection incidence over 20 years. This was illustrated by the fact that not a single new HIV infection occurred within the first year of follow-up in the cohorts recruited from 1998 onwards. There were some reductions in the HCV incidence and prevalence in the same period. This was particularly the case amongst younger and new initiates to injecting. However, older injectors and those with longer injection histories still had practically the same HCV burden.

SMMGP comment: Although the HCV prevalence had dipped a little it hadn't in the older injectors. It may be that this cohort hasn't been running for long enough and that older injectors were infected 20-25 years ago before harm reduction measures hit home. The differences between HIV and HCV are stark. This is a critical point from this paper - these data can be interpreted to suggest that the same measures that have markedly reduced HIV transmission have simply *delayed* HCV transmission. This is the window of opportunity referred to in the accompanying editorial.

Another way of looking at this is to put it in terms of critical levels of needle sharing. Models have suggested that to prevent HIV, needle sharing needs to be reduced to fewer than 17 injecting partners. For HCV this number must be reduced to 3 injecting partners given its higher prevalence and infectivity. Current estimates amongst Australian IDUs suggest it is around 6 injecting partners per year.

The problem is that we would need a dramatic intensification in needle exchange to really address hepatitis C. This alone won't be enough and we need a whole raft of interventions. We need to reduce the overall prevalence pool of HCV by getting more people into treatment, we need to encourage less risky injection practices and perhaps we need to try to take advantage of the delay in infection with HCV in the first few years by targeting this group of younger injectors, or those who haven't yet progressed to injection.

Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow up cohort study *Kuepper R, van Os J, Lieb R, Wittchen H. Hofler M, Henquet C. BMJ 2011;342:d738*

The aim of this study was to look at whether or not cannabis increased the risk of psychotic outcomes by changing the incidence and persistence of subclinical expression of psychosis in the general population. They used data from a prospective cohort study based in Germany. In total they had 1923 individuals who were aged 14 to 24 at baseline. The main outcome measures were the incidence and persistence of subthreshold psychotic symptoms. They assessed cannabis use and psychotic symptoms at baseline, 3.5 years (T2) and 8.4 years (T3).

The results showed that, overall, the incidence rate of psychotic symptoms over the period from baseline to T2 was 31% in exposed individuals versus 20% in non-exposed individuals. Between T2 and T3 the respective risks for exposed and non-exposed individuals were 14% and 8%. There was evidence of something of a dose response relationship with longer exposure to cannabis showing a greater risk of persistent psychotic experiences.

SMMGP comment: This 10 year cohort study showed that 'cannabis use significantly increased the risk of incident psychotic experiences'. This association seemed to be independent of all the other variables thrown at it and there was also no evidence of use of cannabis as self-medication.

The accompanying BMJ editorial fleshes out some of the arguments here. This is further evidence, and refutes some of the suggestions, that this association is related to confounding or to do with self-medication. The editorial quotes likely absolute risks for psychosis increasing from around 7 in 1000 non-cannabis to about 14 in 1000 for regular users but they do add the caveat that the risks could be significantly greater in those where there are additional risk factors, such as having a first-degree relative affected.

Psychosocial treatments for cocaine dependence: the role of depressive symptoms. *Stulz N, Thase ME, Gallop R, Crits-Christoph P. Drug Alcohol Dep 2011;114:41-48*

This study wanted to investigate the association between cocaine use and depression. It did this through further statistical analysis of the data from a study looking at various psychosocial interventions in cocaine dependence.

In this study they started with a total of 487 outpatients who all had a principal diagnosis of cocaine dependence. They had all used cocaine within the previous 30 days and they were randomly assigned to four different treatments for 6 months. The four different treatment groups were: two groups involved professional psychotherapy (either cognitive therapy or supportive-expressive psychodynamic therapy) alongside group drug counselling; the third group received individual drug counselling alongside group drug counselling; and the fourth got group drug counselling only.

More than half (55%) of them reported mild-moderate depression at baseline. There were 147 patients who were diagnosed with mood disorders and 139 of these as cocaine-induced mood disorder. The results indicated that there was a moderate but statistically significant ($p<0.01$) influence of depression severity on increased drug use in the upcoming month but it was noted that drug use did not predict future depression severity. There were no significant differences between the different psycho-social treatments in terms of drug use or depression severity during treatment.

SMMGP comment: One has to take a deep breath before launching in to critically appraise a study in which the statistical method involves a 'hybrid latent growth model'. Ultimately, the study showed no clear difference between the interventions but there are some interesting wrinkles around the issue of depression.

The results suggested that there was a statistically significant influence of depression on increased drug use in the upcoming month. In other words, this means that depression symptoms are an important predictor of drug use outcomes during psychosocial treatments. This flies in the face of any assumption that the depression in stimulant users is drug-induced and it also suggests we should be making specific efforts to target depression in cocaine dependence to improve outcomes.

Some of us had the privilege to go to a seminar by Jim Orford on *'Time to Ask the Right Questions in the Right Way: A New Direction for Addiction Treatment Research?* ' where we discussed different treatment, trials and much more but one of the many things we learnt was that we probably need to stop studying named techniques and focus instead on studying change processes and developing good, general addiction change theories.

When we apply this approach to this paper then the different patient groups are probably irrelevant and clinician's approach (for example credible, knowledgeable, concerned, effective helpers who developed a working alliance) is more important.

Cessation of groin injecting behaviour among patients on oral opioid substitution therapy.
Senbanjo R, Hunt N, Strang J. Addiction 2011;106:376-382

This study's aim was to identify factors that might influence cessation of groin injecting among people receiving opioid substitution therapy. It was a cross-sectional survey among drug treatment centres in the South East of England. They recruited the 114 participants when they attended an ultrasound 'health check'. As part of the assessment they were able to scan and classify the condition of the vessels in the femoral vein and artery.

In a total of 216 groin scans there was significant vein damage identified in 72.5%. The grade of femoral vein damage was strongly correlated with 'moderate to severe' chronic venous disease (CVD). In those who stopped groin injecting (n=49) their behaviour change was attributed to effective treatment (30.6%), health complications (28.6%) and health-risk concerns (20.4%).

Those who had given up groin injecting tended to be older and had been injecting and in treatment for longer. The results showed that other factors associated with groin injecting cessation were history of deep vein thrombosis ($p<0.05$), septicaemia ($p<0.05$), moderate/severe chronic venous disease ($p<0.01$) and 'very severe' femoral vein damage on ultrasonography.

SMMGP comment: The study draws an interesting distinction between the 'last resort' groin injectors – those who have exhausted their venous options; and 'convenience' groin injectors. In their sample 84% started groin injecting when they ran out of other surface veins but the rest had chosen to groin inject for other reasons. One under-reported area, but which will be well recognised by clinicians, is the impact of chronic venous disease (CVD) in groin injectors. This study showed a relatively low prevalence of 'moderate to severe' CVD at 20.2% in either leg. This might be low compared with previous studies (which have been as high as nearly 58%) but given the relatively young age of those with CVD this still represents an appalling disease burden carried by this group.

Nearly one-third of groin injectors may be stopping as a response to oral substitution therapy and this certainly points toward the need to optimise treatment whenever possible. The authors finish by commenting on the intractable nature of groin injecting and that effective measures to get the majority to stop before they run into serious physical harm are sorely lacking.

"Should I stay or should I go?" Coming off methadone and buprenorphine treatment.
Winstock AR, Lintzeris N, Lea T. Int J Drug Policy 2011;22:77-81

This was a cross-sectional survey of 145 people receiving opiate substitution therapy at public clinics in Sydney, Australia. The aim of the study was to 'investigate patient perspectives regarding coming off maintenance opioid substitution treatment (OST)'.

The mean daily dose of methadone was 71.4mg and for buprenorphine or buprenorphine-naloxone it was 13.4mg. Those on methadone had been in treatment longer (33 months vs 17 months) and in the preceding 3 months 41% on buprenorphine had reduced their dose compared with 18% of those on methadone.

The results showed that 62% reported high interest in coming off treatment in the next 6 months. These people with high interest showed an association with having discussed treatment, not citing concern about heroin relapse, and shorter duration of current treatment episode. Overall, 71% reported previous withdrawal attempts and 23% had achieved abstinence from opioids for ≥3 months following a previous withdrawal attempt.

Participants were asked to choose from a list of options and endorse three methods they would be 'most interested in trying on their next withdrawal attempt'. The top three were doctor-controlled gradual reduction (68%), self-controlled gradual reduction (41%), and switch to buprenorphine from methadone (27%). In the middle were counselling (17%), other medication for outpatient detoxification (17%), inpatient detoxification (14%), and rapid naltrexone detoxification (10%). The methods scoring lowest were residential rehabilitation for ≥1 month (10%), Narcotics Anonymous (8%) and 'jump off' (8%).

The biggest concerns reported about withdrawal were withdrawal discomfort (68%), increased pain (50%), and relapse to heroin use (48%).

SMMGP comment: In their introduction the authors comment that the literature has demonstrated that longer treatment duration is associated with better long-term drug and outcomes. They then go on to point out how this has meant that treatment retention has become a surrogate marker for treatment success. Surrogate markers should always be held up for close inspection – it's been a classic Big Pharma ruse for years to use them to obfuscate. Keeping people in treatment is not an end in itself in the same way that cholesterol levels are not always a suitable clinical endpoint for statin therapy. This is a helpful study to quantify some of the desired outcomes for those on opiate substitution therapy. Ultimately, it perhaps has less value in the consultation where each individual's needs and wishes should be considered. It is worth noting as well that over one-third of the sample didn't express any interest in stopping in the next 6 months. There is no doubt we need to keep discussing this issue with everyone in treatment but it is also important that the discussions have no coercive sub-text.

Prescribing is just one aspect of treatment and the newly published *Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care* is now available for download at the SMMGP website.

Unintended pregnancy in opioid-abusing women. *Heil SH, Jones HE, Arria A, et al. J Sub Abuse Treat 2011;40:199-202*

This modest US study looked at the important topic of unintended pregnancy in opioid-abusing women. They recruited 946 opioid-abusing pregnant women, both new to treatment and already in treatment, who were screened as part of a multisite randomised controlled trial into methadone and buprenorphine during pregnancy.

As part of the interview pregnancy intention was assessed with the question "When did you intend to become pregnant?" and the response options were "sooner", "now", "later", "never", and "don't know/unsure". This then allowed the researchers to place the women and their pregnancies into several different categories. The results could then be presented as three major 'subtypes' of unintended pregnancy and these were: 'mistimed' (34%); 'unwanted' (27%); and 'ambivalent' (26%).

In total 86% of pregnancies could be classified as unintended. Women with unintended pregnancies were more likely to have used cocaine in the past 30 days prior to screening compared to women with intended pregnancies. More than 90% of the sample had a history of prior drug use and they averaged more than three episodes of treatment.

SMMGP comment: This might be a relatively short report but it can mine a rich seam when it comes to formulating policy and practice for women in treatment. There is also the potential for considerable controversy.

The study shows that nearly 9 out of 10 the pregnancies were unintended. That should be

enough to make those of us delivering services wince. The first question that might pop into your head is about the rate of unintended pregnancies in the general population. The authors have looked at the literature and the evidence suggests that 31-47% of pregnancies are unintended. So, the rate of unintended pregnancies in women using opioids in the US is around two to three times greater.

The authors suggest that 'interventions are sorely needed' and it also goes on to suggest that one strategy would be to integrate free family planning services into drug treatment programs. This was an American study so the issue of where women access care is a real issue and their repeated attendance at drug treatment centres makes for an obvious opportunity to integrate services. Here in the UK we already have a model that could do exactly this and integrate drug treatment with free family planning – this is exactly what general practice in the NHS can and does offer.

This issue was discussed in Mary Hepburn's great article in SMMGP Network 30 http://tinyurl.com/network30 and she stated: *"Women with problem drug use often have unplanned but not necessarily unintended or unwanted pregnancies. The timing of their pregnancies is however often inappropriate. Addressing the problems related to drug use when the woman is already pregnant is stressful and the scope for improving outcomes is limited but could be avoided or minimised by appropriate planning and management of their drug use and related problems before conception.*

Disappointingly the opportunity to discuss reproductive plans in treatment is often squandered and pregnancies often occur to the surprise to both women and services!

This is of particular concern given that any treatment of addiction, whether pharmacological or psychosocial, may increase fertility either directly or indirectly so, apart from the obvious social benefits, from a purely medico-legal point of view any addictions treatment should be accompanied by information and advice about contraception.

Instead of trying to prevent drug using women from having children (which will be almost invariably unsuccessfully) a more profitable approach would be to help women to address their problems, to explore their aspirations with regard to having children and to ensure any pregnancies they do have are intended and optimally timed for the best possible medical and social outcomes. Primary care services are ideally placed to play a leading role in this area with enormous potential for reducing the impact of problem drug use on the children of drug using mothers and reducing the intergenerational effects of health inequalities. It is an opportunity which should not be missed."

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